

# Weekly High-Dose Calcitriol and Docetaxel in Metastatic Androgen-Independent Prostate Cancer

By Tomasz M. Beer, Kristine M. Eilers, Mark Garzotto, Merrill J. Egorin, Bruce A. Lowe, and W. David Henner

**Purpose:** To determine the safety and efficacy of weekly high-dose oral calcitriol (Rocaltrol, Roche Pharmaceuticals, Basel, Switzerland) and docetaxel (Taxotere, Aventis Pharmaceuticals, Bridgewater, NJ) in patients with metastatic androgen-independent prostate cancer (AIPC).

**Patients and Methods:** Thirty-seven patients were treated with oral calcitriol (0.5  $\mu\text{g}/\text{kg}$ ) on day 1 followed by docetaxel (36  $\text{mg}/\text{m}^2$ ) on day 2, repeated weekly for 6 weeks of an 8-week cycle. Patients maintained a reduced calcium diet and increased oral hydration. Prostate-specific antigen (PSA) response was the primary end point, which was defined as a 50% reduction in PSA level confirmed 4 weeks later.

**Results:** Thirty of 37 patients (81%; 95% confidence interval [CI], 68% to 94%) achieved a PSA response. Twenty-two patients (59%; 95% CI, 43% to 75%) had a confirmed > 75% reduction in PSA. Eight of the 15 patients with measurable disease (53%; 95% CI, 27% to 79%) had a

confirmed partial response. Median time to progression was 11.4 months (95% CI, 8.7 to 14 months), and median survival was 19.5 months (95% CI, 15.3 months to incalculable). Overall survival at 1 year was 89% (95% CI, 74% to 95%). Treatment-related toxicity was generally similar to that expected with single-agent docetaxel. Pharmacokinetics of either calcitriol or docetaxel were not affected by the presence of its companion drug in an exploratory substudy.

**Conclusion:** The combination of weekly oral high-dose calcitriol and weekly docetaxel is a well-tolerated regimen for AIPC. PSA and measurable disease response rates as well as time to progression and survival are promising when compared with contemporary phase II studies of single-agent docetaxel in AIPC. Further study of this regimen is warranted.

*J Clin Oncol* 21:123-128. © 2003 by American Society of Clinical Oncology.

TREATMENT FOR androgen-independent prostate cancer (AIPC) remains unsatisfactory. Chemotherapy with mitoxantrone and prednisone offers a palliative benefit,<sup>1,2</sup> but no treatment has been shown to lengthen survival in a randomized trial. Four phase II clinical trials in patients with AIPC examined single-agent docetaxel given at 75  $\text{mg}/\text{m}^2$  every 3 weeks<sup>3,4</sup> or at 36  $\text{mg}/\text{m}^2$  weekly for 6 of every 8 weeks.<sup>5,6</sup> These data are summarized in Table 1.

Overall, 57 of 138 (42%) patients responded by PSA level and 10 of 36 (28%) patients responded in measurable disease. Time to progression and overall survival, available only for the weekly docetaxel regimens, were 4.6 to 5.1 months and 9.0 to 9.2 months, respectively. This level of activity in AIPC marks docetaxel as a reasonable building block for the development of novel treatment combinations.

Calcitriol is a promising companion agent for docetaxel in AIPC. At supraphysiologic concentrations, this natural ligand for the vitamin D receptor (VDR) or its analogs exerts significant antiproliferative activity on prostate cancer cell lines<sup>7-12</sup> and in animal models of prostate cancer.<sup>9,13</sup>

Calcitriol enhances the antitumor activity of several cytotoxic agents in a number of preclinical tumor model systems. In prostate cancer cell lines, calcitriol enhances antitumor activity of docetaxel,<sup>14</sup> paclitaxel,<sup>15</sup> and platinum compounds.<sup>16</sup> Similar results are seen in prostate cancer animal models with docetaxel (CS Johnson, personal communication) and paclitaxel.<sup>15</sup>

Mechanisms by which calcitriol inhibits cancer cell proliferation and sensitizes cancer cells to cytotoxic agents remain incompletely understood. Calcitriol treatment has been associated with G<sub>0</sub>/G<sub>1</sub> arrest,<sup>17</sup> changes in p21<sup>Waf1</sup> and p27<sup>Kip1</sup> expression,<sup>15,18,19</sup> dephosphorylation of the retinoblastoma protein,<sup>20</sup> downregulation of *bcl-2*,<sup>21</sup> inhibition of angiogenesis,<sup>22,23</sup> and induction of apoptosis.<sup>24</sup> Calcitriol-induced changes in several growth factor systems, including EGF,<sup>25</sup> TGF $\beta$ ,<sup>26,27</sup> and IGF<sup>28,29</sup> have been reported.

Recent work in PC-3 cells demonstrated that 24 hours after treatment with calcitriol, p21<sup>Waf1</sup> expression was reduced and paclitaxel cytotoxicity was enhanced without an increase in apoptosis, whereas at 48 hours, calcitriol accelerated paclitaxel-induced apoptosis.<sup>15</sup> In murine squamous cell carcinoma cells, pretreatment with calcitriol enhanced paclitaxel-mediated apoptosis and synergistically induced MEKK-1.<sup>30</sup>

The supraphysiologic concentrations of calcitriol required for antitumor effects in preclinical models are not achievable in humans with daily dosing of calcitriol because of hypercalcemia and hypercalcuria.<sup>31,32</sup> Intermittent dosing permits substantial escalation of the calcitriol dose. Subcutaneous dosing every other day produced peak blood calcitriol levels of approximately 0.7 nM.<sup>33</sup> In a phase I study of weekly oral administration, peak plasma calcitriol levels of 3.7 to 6.0 nM were reached with minimal toxicity. The recommended dose for phase II trials was 0.5  $\mu\text{g}/\text{kg}$ .<sup>34</sup>

The primary goal of this study was to evaluate the safety and efficacy of a new regimen that combines high-dose oral calcitriol with docetaxel administered on a weekly schedule to patients with AIPC. An exploratory examination of the impact of each agent on the pharmacokinetics of its companion was a secondary goal.

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From the Oregon Health & Science University and Portland VA Medical Center, Portland, OR; and University of Pittsburgh Cancer Institute, Pittsburgh, PA.

Submitted May 16, 2002; accepted September 12, 2002.

Supported in part by grant GIA US 16,066 from Aventis Pharmaceuticals and grant 3M01RR00334 to 33S2 from the National Institutes of Health.

Address reprint requests to Tomasz M. Beer, MD, Department of Medicine, Oregon Health & Science University, Mail Code L586, 3181 SW Sam Jackson Park Road, Portland, OR 97239; email: beert@ohsu.edu.

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0732-183X/03/2101-123/\$20.00

Table 1. Published Studies of Single-Agent Docetaxel in AIPC

Author	Docetaxel Regimen	Dexamethasone Regimen	n	PSA RR	Measurable RR
Picus and Schultz <sup>3</sup>	75 mg/m <sup>2</sup> q 21 days	20 mg po twice starting 24 hours before docetaxel then 8 mg po twice daily for 6 doses	35	46%	7 of 25
Friedland et al <sup>4</sup>	75 mg/m <sup>2</sup> q 21 days	8 mg po twice daily for 5 doses starting 24 hours before docetaxel	21	38%	1 of 6
Berry et al <sup>6</sup>	36 mg/m <sup>2</sup> weekly × 6 every 8 weeks	8 mg po 12 hours before, 1 hour before, and 12 hours after docetaxel	60	41%	NR
Beer et al <sup>5</sup>	36 mg/m <sup>2</sup> weekly × 6 every 8 weeks	8 mg po 12 hours before, 1 hour before, and 12 hours after docetaxel	25	46%	2 of 5

## PATIENTS AND METHODS

### Eligibility Criteria

Men with pathologically proven adenocarcinoma of the prostate, metastases, and evidence of progression (development of new metastatic lesions or an increase in cancer-related pain or a 50% rise in the prostate-specific antigen [PSA] confirmed by a second measurement after 2 weeks) despite standard hormonal management (including antiandrogen withdrawal: 6 weeks for bicalutamide, 4 weeks for flutamide or nilutamide) were eligible. Additional requirements included PSA  $\geq$  5 ng/mL, serum testosterone level less than 50 ng/mL, Eastern Cooperative Oncology Group (ECOG) performance status  $\leq$  3, life expectancy  $\geq$  3 months, age  $\geq$  18 years, and ability to complete pain and quality-of-life questionnaires.

Patients were excluded for prior malignancy within the past 5 years except nonmelanotic skin cancer; significant active medical illness that precluded protocol therapy; history of cancer related hypercalcemia, uncontrolled heart failure, kidney stones within 5 years; investigational therapy within 30 days; prior chemotherapy for prostate cancer; radiotherapy within 1 month or radiopharmaceuticals within 2 months; thiazide diuretics within 7 days; ongoing treatment with magnesium-containing antacids or bile-resin binders; hypersensitivity to drugs formulated with polysorbate-80;  $\geq$  grade 2 peripheral neuropathy; WBC less than 3,000/mm<sup>3</sup>; neutrophil count less than 1,500/mm<sup>3</sup>; platelet count less than 100,000/mm<sup>3</sup>; conjugated bilirubin greater than upper limit of normal (ULN); ALT greater than 2.0  $\times$  ULN; ALT greater than 1.5  $\times$  ULN concomitant with alkaline phosphatase 2.5  $\times$  ULN; creatinine greater than 1.3 mg/dL; calcium greater than 10.5 mg/dL; phosphorus greater than 4.2 mg/dL; and alkaline phosphatase greater than 4.0  $\times$  ULN (except in patients with known bone involvement with cancer and both conjugated bilirubin and ALT in the normal range).

### Evaluations

Pretreatment evaluation included medical history, physical examination, serum PSA, serum testosterone, serum biochemistry, complete blood count, bone scan, and computed tomography (CT) of the abdomen and pelvis. Complete blood counts were obtained before each docetaxel dose. Physical examination, assessment of adverse events, serum PSA, and serum biochemistry were examined every 4 weeks. Serum calcium was checked weekly for the first 4 weeks. If serum calcium remained within the normal range during the first 4 weeks, it was monitored every 4 weeks for the remainder of the study. In patients with measurable disease by CT scan, CT scans were repeated every 8 weeks. Bone scans were repeated as clinically indicated. Routine imaging to detect asymptomatic renal stones was not performed.

### Treatment

Signed, informed patient consent was obtained before any procedures. Primary hormonal therapy was maintained for the duration of the study. Patients maintained a reduced calcium diet during the treatment weeks, restricting daily calcium intake to 400 to 500 mg as previously described.<sup>34</sup> Calcium and magnesium supplements and bile-resin binding agents were prohibited. On days 1, 2, and 3 of each treatment week, patients increased oral hydration by drinking 4 to 6 cups of fluid above their usual intake.

Calcitriol (Rocaltrol 0.5  $\mu$ g capsules, Roche Pharmaceuticals, Basel, Switzerland) 0.5  $\mu$ g/kg was given orally in four divided doses over 4 hours on day 1 followed by docetaxel (Taxotere, Aventis Pharmaceuticals, Bridgewater, NJ) 36 mg/m<sup>2</sup> intravenously over 15 to 30 minutes on day 2 of each treatment week. Treatment was administered weekly for 6 consecutive weeks

on an 8-week cycle. Premedication with dexamethasone 8 mg orally 12 hours and 1 hour before docetaxel infusion and 12 hours after docetaxel infusion was given. Patients were routinely asked during follow-up visits whether they were able to take all the calcitriol pills.

Therapy with both agents was withheld for platelet count less than 75,000/mm<sup>3</sup> or neutrophil count less than 1,000/mm<sup>3</sup>. The dose of docetaxel was reduced by 25% if recovery of platelet or neutrophil count took longer than 1 week, if multiple consecutive doses needed to be withheld, if patients experienced febrile neutropenia, or for Aspartate Transaminase (AST) of 1.6 to 5  $\times$  ULN when bilirubin remained in the normal range and alkaline phosphatase was  $\leq$  5  $\times$  ULN. Therapy was withheld for bilirubin greater than ULN, alkaline phosphatase more than 5  $\times$  ULN unless both ALT and bilirubin remained normal, or ALT more than 5  $\times$  ULN. Therapy was resumed at a 25% dose reduction in patients whose liver function tests recovered within 3 weeks. Dose reductions of 10% to 25% for fatigue were permitted at the discretion of the treating physician.

Treatment was administered until progression, patient request to withdraw, or unacceptable toxicity. Responding patients who reached a PSA less than 4 ng/mL were permitted to receive therapy intermittently. These patients continued PSA monitoring and restarted therapy when their PSA increased by 50% and at least 1 ng/mL. The study was approved by the institutional review boards of Oregon Health & Science University and Portland VA Medical Center.

### Assessment of Outcome

The primary end point was PSA response defined as a 50% reduction in PSA maintained on two consecutive evaluations at least 4 weeks apart.<sup>35</sup> Secondary end points included response in measurable disease by response evaluation criteria in solid tumors (RECIST) criteria,<sup>36</sup> time to progression, toxicity (National Cancer Institute Common Toxicity Criteria version 2.0), survival, and calcitriol and docetaxel pharmacokinetics in a subset of patients. Progression was defined as a confirmed increase in the PSA of 50% above nadir (minimum increase of 1.0 ng/mL), progression in measurable disease as defined by RECIST criteria, or the appearance of new lesions on bone scan that were not thought to be related to either tumor flare, trauma, or other nonmalignant cause. Time to progression was defined from the first day of treatment until the first finding subsequently confirmed to be progression.

### Statistical Design

Sample size was chosen with the goal of detecting a 20% increase in the PSA response rate over that seen with single-agent weekly docetaxel (from an estimated 40% to 60%). A two-stage study minmax design, with  $\alpha = 0.05$  and power of 80% would reject the regimen if fewer than 17 of 34 patients responded in the first stage and would require a total of 39 patients.<sup>37</sup>

A docetaxel dose de-escalation was planned in the event of an unexpected increase in toxicity resulting from the combination of the two agents. A de-escalation schema developed by Blanke et al<sup>38</sup> was used. Briefly, toxicity was assessed after the first six and 12 patients completed cycle 1 of therapy. Docetaxel dose de-escalation to 30 mg/m<sup>2</sup>, then to 27 mg/m<sup>2</sup>, and finally to 24 mg/m<sup>2</sup> was planned if five of the first six or nine of the first 12 patients experienced a grade 3 or greater treatment-related toxicity.

### Pharmacokinetics Substudy

An exploratory pharmacokinetic substudy was carried out in five patients. Patients received calcitriol only in week 0, docetaxel only in week 1, and

both in weeks 2 to 6. Participation in the substudy therefore extended the substudy cycle of treatment (ie. that cycle of treatment during which the pharmacokinetic data were collected) by 1 week. Calcitriol levels were drawn at 0, 2, 4, 6, 24, and 48 hours as previously described.<sup>34</sup> Docetaxel levels were drawn before infusion, immediately after infusion, and after 15 minutes, 45 minutes, 3 hours, 6.5 hours, and 24 hours.

Calcitriol levels were measured by radioimmunoassay as described by Hollis et al.<sup>39</sup> The maximum calcitriol concentration ( $C_{max}$ ) and time of maximum calcitriol concentration ( $T_{max}$ ) were determined by visual inspection. The area under the curve (AUC) was calculated using the linear trapezoidal rule. The adjusted plasma concentration (baseline, or physiologic calcitriol level subtracted from all points) results were analyzed by noncompartmental methods.

Concentrations of docetaxel in patient plasma were determined with a recently developed liquid chromatography/mass spectrometry assay. One-milliliter samples of human plasma were placed into 1.5-mL microcentrifuge tubes. Ten  $\mu$ L of a 1- $\mu$ M solution of paclitaxel internal standard in methanol were added to each tube, and the tubes were vortexed briefly. Samples were prepared for high-performance liquid chromatography (HPLC) analysis using a previously described solid phase extraction method.<sup>40</sup> Each dried residue was redissolved in 100  $\mu$ L of methanol:distilled water (70:30, vol/vol), vortexed briefly, transferred to HPLC autosampler vials, and 10  $\mu$ L were injected into the LC/MS system. The HPLC consisted of an Agilent model 1,100 Autosampler (Agilent Technologies, Palo Alto, CA), an Agilent 1,100 Quaternary pump, and a Hypersil C18 (ODS) (5  $\mu$ m, 100  $\times$  2 mm) analytical column (Phenomenex, Torrance, CA). The isocratic mobile phase, consisting of 0.1% formic acid in methanol:water (70:30, vol/vol), was pumped at 0.2 mL/min; the run time was 7 minutes. Column eluate was analyzed with a ThermoFinnigan aQa Mass Spectrometer (ThermoQuest, San Jose, CA) operating in electrospray, positive-single-ion mode to monitor 808.1 m/z for docetaxel and 854.0 m/z for paclitaxel. The insert probe temperature was set at 250°C with 5,000 V applied as the ion spray voltage and 10 V as the orifice voltage. Nitrogen gas flow was fixed by the tank head unit set at 75 psi (520 kPa). The system was operated with ThermoFinnigan Excalibur Software. The internal standard ratio was calculated by dividing the analyte peak area by the peak area of the internal standard. Standard curves of docetaxel were constructed by plotting the IS ratio versus the known concentration of analyte in each sample. Standard curves were fit by linear regression with weighting by  $1/yr$ ,<sup>2</sup> followed by back calculation of concentrations. Docetaxel concentrations in patient samples were calculated by comparing the IS ratio measured for each sample to the weighted, linear function derived from a concomitantly performed standard curve that related the IS ratio to docetaxel concentration. The  $AUC_{0-\infty}$  and elimination half-life for the populations receiving docetaxel alone and docetaxel administered after calcitriol were estimated by fitting all available docetaxel measurements for each population to a three-compartment model by multiexponential regression (WinNonlin Pro, 1.5, Pharsight Corp., Mountain View, CA).

## RESULTS

### Patient Characteristics

Thirty-nine men were recruited between May 2000 and May 2001. Two were ineligible: One patient had locally advanced AIPC but no metastases; the other patient had severe cancer-related syndrome of inappropriate antidiuretic hormone secretion (SIADH) before registration, and the fluid restriction required for the treatment of SIADH was incompatible with the hydration required by the protocol. Results for the 37 eligible patients are reported. Pretreatment characteristics are summarized in Table 2. Briefly, the median age was 73 (range, 46 to 83). Median ECOG performance status was 1. The median PSA was 99 ng/mL (range, 6 to 921 ng/mL). All patients had radiographic evidence of metastatic disease: Ninety-two percent of patients had bone metastases and 41% had measurable metastases, all to lymph nodes. Fifty-one percent of patients had received prior radiation either to the primary tumor or to a metastatic site. In addition to prior hormonal therapy, six patients had received prior experimental therapy. No patients received prior cytotoxic chemother-

**Table 2. Patient Characteristics on Entry**

Characteristic	No. of Patients
No. of patients	37
Age, years	
Median (range)	73 (46-83)
ECOG performance status	
0	13
1	15
2	8
3	1
PSA (ng/mL)	
Median (range)	99 (6-921)
Alkaline phosphatase (u/L)	
Median (range)	127 (41-1304)
Site of metastases	
Bone only	22 (59%)
Bone and lymph nodes	12 (32%)
Lymph nodes only	3 (8%)
Prior radiation	
External beam radiation to primary	17 (46%)
External beam radiation to metastases	8 (22%)
Radiopharmaceuticals	1 (3%)
No. of prior hormonal therapies for prostate cancer	
1	6 (16%)
2	23 (62%)
3	8 (22%)

apy. The median follow-up from the first day of treatment is 17 months (range, 11 to 23 months).

### Treatment

Median duration of treatment was 43 weeks (range, 8 to 93+ weeks). Therapy was discontinued because of progression in 18 patients, toxicity in three patients, physician or patient preference in three patients, and death from unrelated causes in two patients. Eleven patients remain on treatment, for a median of 54 weeks (range, 29 to 93 weeks). Nine patients chose intermittent chemotherapy after reaching a PSA less than 4 ng/mL. To date, therapy has been resumed in four of these patients after a break that ranged from 16 to 23 weeks.

### Toxicity

Treatment was generally well tolerated. There was one treatment-related death from pneumonia. Bronchoscopic alveolar lavage did not identify a specific organism in this patient, and no lung biopsy was obtained.

Grade 3 or greater treatment-related toxicity is detailed below. Forty-one percent had leukopenia, 24% had neutropenia, and 3% had anemia. No episodes of neutropenic fever were observed. The most common nonhematologic toxicity, seen in 24% of patients, was hyperglycemia, expected with the standard dexamethasone premedication. Peptic ulcer was seen in 11% of patients, and pneumonia in 8%. In addition, the following toxic effects were seen once: edema, anorexia, dyspnea, hypocalcemia, intravenous catheter-related infection, *Clostridium difficile* colitis, AST elevation, bronchiolitis obliterans organizing pneumonia, angina, and deep venous thrombosis.

Hypercalcemia was seen in three patients; grade 1 ( $>$  ULN-11.5 mg/dL) in two patients and grade 2 (11.6 to 12.5 mg/dL) in one patient. All episodes resolved without intervention, and no calcitriol doses were withheld or reduced. No patient developed

Table 3. Pharmacokinetic Parameters of Calcitriol With and Without Docetaxel

	Calcitriol (C) Alone		Calcitriol with Docetaxel (C with D)		Difference* (C-C with D)		Pt
	Mean	Range	Mean	Range	Mean	Range	
C <sub>max</sub> , pg/mL	836	562 to 1154	864	486 to 1185	-81	-385 to +216	.51
AUC <sub>0-24</sub> , pg · hr/mL	11554	8166 to 16009	11610	6574 to 14942	-823	-4714 to +2746	.66
AUC <sub>0-∞</sub> , pg · hr/mL	14512	11163 to 19859	14677	8862 to 17799	-800	-6617 to +3286	.68
T <sub>1/2</sub> (h)	10.2	8 to 12	10.7	8 to 12	-0.46	-3 to +1	.48

\*Inpatient difference calculated with each patient serving as his own control.

†Paired *t* test performed on the inpatient difference in each parameter.

symptomatic urinary calculi. The incidence of asymptomatic urinary calculi was not determined. The single episode of grade 2 hypercalcemia occurred after a patient ingested a full dose of calcitriol 2 days in a row in error. Six patients developed grade 1 creatinine elevations (highest, 1.5 mg/dL). Therapy was not withheld, and all six patients had a normal creatinine concentration at the next measurement. Compliance with dietary calcium restriction and hydration recommendations was not monitored, and the contribution of these recommendations to the safety of this regimen was not examined.

Twenty of 37 patients had their docetaxel dose reduced after a median of 17 weeks of therapy. Reasons for dose reduction included fatigue in 10 patients, liver function abnormalities in four patients, hematologic toxicity in three patients, and peptic ulcer, dermatitis, and neuropathy in one patient each. In patients who had a dose reduction, the median dose was reduced to 75% of the starting dose.

#### PSA Response to Therapy

Thirty of 37 patients (81%; 95% confidence interval [CI], 68% to 94%) achieved a confirmed PSA response. Twenty-two patients (59%; 95% CI, 43% to 75%) had a confirmed greater than 75% reduction in the PSA with treatment. Ten patients (27%; 95% CI, 13% to 42%) achieved a confirmed PSA less than 4 ng/mL. The median time to first PSA less than 50% of baseline was 8 weeks (range, 4 to 45 weeks). Of the 30 PSA responders, five had a transient initial rise in the PSA (median, 8.3%; range, 1% to 29%) before their PSA reduction. Of the seven patients who did not have a confirmed PSA response, five had stable disease for 3.7 to 8.7 months.

#### Response in Measurable Disease

Fifteen patients had measurable disease, all involving lymph nodes. Confirmed partial response was observed in eight (53%; 95% CI, 27% to 79%). Of the remaining patients, one was not assessable because he was removed from the study for toxicity after only 8 weeks of treatment, and six patients had confirmed stable disease. The median duration of stable disease was 8.1 months (range, 6 to 13.7 months).

#### Bone Scan Findings

All patients had a pretherapy bone scan. Twelve patients had a total of 15 posttherapy bone scans. Three of these scans were obtained after PSA progression; two showed stable disease and one had a new lesion. Twelve scans were obtained during therapy in patients without PSA progression. Seven of these scans were ordered to evaluate new pain. One showed new bone lesions and led to the diagnosis of progression. Six scans did not demonstrate disease progression. Five scans were ordered to

followup disease in responding patients without new pain. None of these scans showed disease progression, although one was thought to represent scintigraphic flare. It is possible that asymptomatic progression of bone disease escaped detection in some patients on this study. However with regular clinical, PSA, and CT follow-up, this is unlikely.

#### Time to Progression and Survival

Progression was first detected by PSA in all but one patient. One patient had a symptomatic bone metastasis confirmed by bone scan before PSA progression. The median time to progression was 11.4 months (95% CI, 8.7 to 14 months). Freedom from progression at 1 year was 46% (95% CI, 29% to 62%). Median overall survival was 19.5 months (95% CI, 15.3 months to incalculable). Overall survival at 1 year was 89% (95% CI, 74% to 95%).

#### Pharmacokinetics

Calcitriol levels were obtained in five patients both without docetaxel and, in a subsequent week, with docetaxel. Inpatient differences between calcitriol pharmacokinetics with and without docetaxel were compared using a paired *t* test. Table 3 provides a summary of these data. No obvious changes in calcitriol C<sub>max</sub>, AUC, or elimination half-life were seen. These results are limited by the small number of patients and limited sampling strategy and, therefore, should be regarded as exploratory.

For docetaxel alone, the population AUC<sub>0-24</sub> was 309 nmol/L × hour and AUC<sub>0-∞</sub> was 343 nmol/L × hour. For docetaxel with calcitriol, the population AUC<sub>0-24</sub> was 307 nmol/L × hour and AUC<sub>0-∞</sub> was 343 nmol/L × hour. The elimination half-life was 9.7 hours for docetaxel administered alone and 10.1 hours for docetaxel administered after calcitriol.

## DISCUSSION

The activity of the calcitriol plus docetaxel regimen for AIPC reported here is encouraging. Whether measured by PSA response rate, incidence of greater than 75% reduction in PSA, time to progression, or overall survival, the results compare favorably with those reported in contemporary phase II trials of single-agent docetaxel in AIPC (Table 1). Activity in measurable disease also appears higher than that expected with docetaxel alone, although this trial as well as the available trials of single-agent docetaxel examined only a small number of such patients. Although these results are encouraging, in the absence of a randomized design it is impossible to exclude the possibility that patient selection or chance contributed to this finding.

The contribution of dexamethasone given as three 8-mg doses over 24 hours once a week to the activity of this regimen is

unknown. The dexamethasone regimen used in this study was identical to that reported in studies of weekly docetaxel in AIPC.<sup>5,6</sup> The addition of calcitriol was, therefore, the only new variable in this regimen. Enhancement of calcitriol-mediated antineoplastic activity by dexamethasone in preclinical systems has been reported.<sup>41,42</sup> Therefore, it is possible that the observed results were a product of a complex interaction among calcitriol, docetaxel, and dexamethasone.

The regimen was well tolerated. No obvious increase was seen in toxicity compared with phase II trials of docetaxel alone, with the possible exception of a somewhat higher than expected incidence of gastric and duodenal ulceration. The dietary calcium restriction and the hydration requirement were modeled after the phase I study of weekly calcitriol.<sup>34</sup> The dietary contribution to the safety of this regimen remains uncertain. Future studies should seek to determine if these dietary recommendations contribute to the safety of treatment with calcitriol and docetaxel. Toxicity comparisons with other phase II trials are complicated by a significant difference in total exposure to chemotherapy. Median duration of therapy in this trial was more than twice as long (10 months) than in trials of weekly docetaxel alone (approximately 4 months).

Preclinical evidence suggests that the approach taken in this clinical trial may be applicable to other malignancies. In addition

to prostate cancer, antiproliferative activity of VDR ligands has been reported in cancers of the breast,<sup>43</sup> lung,<sup>44</sup> bladder,<sup>45</sup> colon,<sup>46</sup> pancreas,<sup>47</sup> endometrium,<sup>48</sup> myeloid leukemia,<sup>49</sup> melanoma,<sup>50</sup> sarcomas of the soft tissues,<sup>51</sup> bone,<sup>52</sup> and others. In experimental systems, VDR ligand-mediated potentiation of cytotoxic agents is not limited to prostate cancer. Such interactions have been described with several chemotherapy agents in preclinical models of squamous cell carcinoma,<sup>53</sup> breast cancer,<sup>54,55</sup> and myeloid leukemia.<sup>56</sup>

In summary, weekly docetaxel coupled with weekly high-dose calcitriol has produced potentially promising results in this phase II trial in AIPC, and the regimen merits further study. Until confirmed in a randomized trial, however, these results should be regarded as hypothesis generating rather than as definitive. A placebo-controlled, double-blinded, randomized comparison of docetaxel plus calcitriol to docetaxel alone is under way and will provide more definitive data.

#### ACKNOWLEDGMENT

We thank Dr Bruce Hollis, PhD, for measuring calcitriol levels; Gilbert Lam, PhD, for assistance with analysis of the pharmacokinetic data; and Scott Cruickshank, MS, for statistical advice. Calcitriol was supplied by Roche Laboratories, Inc.

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